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August 5, 2015

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ASSISTANCE REQUESTED: Detailed clarification regarding how to account for differing toxicity potencies between the surrogate chemical (i.e., technical chlordane) and the requested chemicals (i.e., *cis*-nonachlor, *trans*-nonachlor, and oxychlordane)

ENCLOSED INFORMATION: Attachment 1: pCBSA review_final.pdf

BE ADVISED: *Unless specifically indicated to have been peer reviewed, it is to be noted that the attached Provisional Toxicity Value Paper(s) have not been through the U.S. EPA's formal review process; therefore, they do not represent a U.S. EPA verified assessment.*

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Supported by Highlight Technologies, LLC, under
U.S. Environmental Protection Agency Contract No. EP-C-13-007

Issue

This supplemental document provides a detailed clarification regarding how to account for differing toxicity potencies between the surrogate chemical (i.e., technical chlordane) and the requested chemicals (i.e., *cis*-nonachlor, *trans*-nonachlor, and oxychlordane).

Background

Our earlier analysis using the Wang et al. (2012) approach (presented in our previous response) identified technical chlordane as an appropriate surrogate for the requested data-poor chemicals, for both noncancer and cancer effects. From the available data, specifically the data from Bondy et al. (2000, 2003), it was clear that oxychlordane was more potent compared to *trans*-nonachlor (8-10 times as described by the authors), and *trans*-nonachlor is more potent than *cis*-nonachlor or technical chlordane, with respect to mortality, in rats exposed to these chemicals for up to 28 days. Though chlordane is an appropriate surrogate for the requested chemicals, because of differences in toxicity potencies, it was indicated in our earlier analysis to consider the relative potencies of these compounds to chlordane when deriving surrogate points of departure (PODs) based on the IRIS assessment for technical chlordane (U.S. EPA, 1997).

Method

To account for the potency differences, a relative potency factor (RPF) can be determined for chemicals with few toxicity data that are structurally similar and have similar dose-response curves for a common endpoint (Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures [U.S. EPA, 2000]; Wang et al. 2012). The requested chemicals (i.e., *cis*-nonachlor, *trans*-nonachlor, and oxychlordane) and technical chlordane meet the above criteria, with similar modes of action (Bondy et al., 2000, 2003, 2005), and the limited available data for the requested chemicals make this a good case to determine RPFs.

A RPF is calculated as a ratio of the dose of an index chemical to another chemical at an *iso*-effective (equivalent toxicity response) dose as presented below (U.S. EPA, 2000). An index chemical is typically the best studied component in a potential mixture.

$$RPF = (ED_x \text{ of index chemical}) / (ED_x \text{ other chemical})$$

where, ED_x = iso-effective Dose (e.g., ED_{50})

In this case, technical chlordane is the index chemical because it is the surrogate chemical based on which surrogate PODs for the requested chemicals are derived (according to Wang et al., 2012 as detailed in previous response). Benchmark dose modeling (BMD) was applied to identify iso-effective doses (BMD_{50}s) at a benchmark response (BMR) of 50%.

Data quality and RPF derivation

The current database for the requested chemicals is limited to only a few relevant toxicity studies (see Table B-3 in the previous response). Among the toxic effects, hepatocyte hypertrophy was identified as the most sensitive and common toxic effect induced by all the requested chemicals

and chlordane (Bondy et al., 2000, 2003), therefore the RPFs were derived based on this effect. Male rats treated with *cis*-nonachlor, and rats of both sexes treated with *trans*-nonachlor showed incidences of hepatocellular hypertrophy at multiple tested doses, whereas technical chlordane and oxychlordane induced this effect only at one of the tested doses. With awareness of these inconsistencies in the dose-responses, the hepatocyte hypertrophy data were subjected to BMD modeling (using BMDS 2.6.0.1 software) to determine the iso-effective doses (BMD_{50}s) for technical chlordane and each of the requested chemicals. As summarized in Table S1, *cis*-nonachlor (males) and *trans*-nonachlor (both sexes) had hepatocyte hypertrophy incidence data of 0% (0/7), 15% (1/7), 29% (2/7), 43% (3/7), 57% (4/7), or 100% (4/4 or 7/7), and *cis*-nonachlor (females), technical chlordane (both sexes), and oxychlordane (females) had 0, 90, or 100% incidence. Therefore, a benchmark response (BMR) of 50% is in the middle of the distribution of these incidences for all the chemicals, and a BMD_{50} is best supported by the data.

When there are multiple adequately fitting models available for each data set, an average of the BMD50s of all the adequately fitting BMD models was used to derive RPFs for each chemical, as presented in Table S2. This is especially important for the chemicals (e.g. technical chlordane, cis-nonachlor, and oxychlordane) with only two data points [0%, 90% or 100%] on the dose-response curve, resulting in low confidence in the estimated BMD_{50}.

The RPFs provide a quantitative estimate for reconciling differences in toxicity potencies of the surrogate chemical and the requested chemicals. The RPFs show that the requested chemicals are more potent and would have lower surrogate PODs compared to the POD of technical chlordane. However, confidence in the RPFs is low because of lower confidence in the BMD_{50} of technical chlordane (which is the index chemical for all the RPF calculations) as described above. Additionally, it should be noted that the RPFs are derived based on a 28-day treatment and might not reflect relative potency differences at longer-term/chronic treatment durations.

Table S1: Incidence of hepatocyte hypertrophy in rats gavaged for up to 28 days					
	Dose (mg/kg-day)				
Treatment	**0**	**0.25**	**1.0**	**2.5**	**25**
Female rats					
Technical Chlordane[a]	**0/7**	**0/7**	**NT**	**0/7**	**7/7***
***cis*-Nonachlor[a]**	**0/7**	**0/7**	**NT**	**0/7**	**6/6***
***trans*-Nonachlor[a]**	**0/7**	**2/7**	**NT**	**7/7***	**4/4***
Oxychlordane[b]	**0/10**	**0/10**	**0/10**	**9/10***	**NT**
Male rats					
Technical Chlordane[a]	**0/7**	**0/7**	**NT**	**0/7**	**7/7***
***cis*-Nonachlor[a]**	**0/7**	**1/7**	**NT**	**3/7**	**7/7***
***trans*-Nonachlor[a]**	**0/7**	**2/7**	**NT**	**4/7**	**7/7***

[a]Bondy et al. (2000)
[b]Bondy et al. (2003)

NT = not tested
*Significantly different from incidence in control group ($p \leq 0.05$) based on Fisher Exact test

Table S2: Derivation of RPFs		
Treatment	**Average BMD_{50} (mg/kg-day)**	**RPF = (Average BMD_{50} of Index Chemical[a]) / (Average BMD_{50} of requested chemical)**
Female rats		
Technical Chlordane	12.22	**1.0**
cis-Nonachlor	12.27	**1.0**
trans-Nonachlor	0.38	**32.2**
Oxychlordane	2.19	**5.6**
Male rats		
Technical Chlordane	12.22	**1.0**
cis-Nonachlor	2.52	**4.8**
trans-Nonachlor	1.64	**7.5**

[a]Technical chlordane

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U.S.EPA. Integrated Risk Information System: Toxicological Review of Chlordane (Technical) (Cas No. 12789-03-6). Washington D.C.: U.S. EPA, 1997.

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